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# Carbohydrate antigen 19-9 as a prognostic biomarker in pancreatic neuroendocrine tumors

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**Abstract.** Carbohydrate antigen 19-9 (CA19-9) is not generally considered to be a biomarker in pancreatic neuroendocrine tumors (pNETs), as the majority of pNETs present with a normal range of CA19-9. The present study aimed to evaluate the role of serum CA19-9 levels as a prognostic factor in a relatively large number of patients with pNETs. Consecutive patients were retrospectively collected from a single institution between June 2006 and February 2015. The receiver operating characteristic (ROC) curve and the area under the ROC curve were used to select the cut-off values for the baseline CA19-9 levels. The primary end point was set as overall survival. Potential factors associated with the abnormal elevation of CA19-9 expression levels in pNETs were also investigated. The cut-off value for CA19-9 was 16 U/ml as determined by the ROC curve, and for the area under the ROC curve it was 0.68. In total, 32.7% of patients (51/156) had CA19-9 expression levels higher than the cut-off value. Univariate analysis demonstrated that CA19-9 >16 U/ml was an adverse prognostic factor for patients' overall survival. The CA19-9 >16 U/ml group had a statistically higher proportion of tumor node metastasis (TNM) stage III or IV, as compared with the CA19-9 ≤16 U/ml group. To the best of our knowledge, the present study is the first to demonstrate that CA19-9 is a prognostic biomarker of pNETs, one that may reflect its aggressiveness and severity.

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## Introduction

Pancreatic neuroendocrine tumors (pNETs) are tumors arising from the endocrine cells of the pancreas; pNETs comprise <3% of novel pancreatic neoplasms (1). Its incidence has increased in recent years since the introduction of novel diagnostic procedures (2). pNETs can be generally divided into functional and nonfunctional tumors. Nonfunctional pNETs constitute ~85% of all pNETs and are more aggressive compared with the functional pNETs (1,3). Although they are generally viewed as indolent tumors, pNETs are highly heterogenous neoplasms and certain subgroups may demonstrate aggressive characteristics (4,5). Currently, therapeutic methods for pNETs are diverse, including surgical resection and non-surgical interventions (targeted therapies, chemotherapy, somatostatin analogues, peptide receptor radionuclide therapy and liver-directed therapies) (6-8). Close observation may be required to small pNETs (9,10). Therefore, biomarkers that reflect the aggressive features of pNETs are urgently required in order to aid therapeutic decisions and follow-up observations (11).

Carbohydrate antigen 19-9 (CA19-9) is a tumor-associated carbohydrate biomarker that was derived from a human colorectal cancer cell line targeted by the monoclonal antibody 1116-NS-19-9 (12). It has been widely used in the management of gastrointestinal malignancies, particularly for pancreatic cancer (11,13). In a pool data analysis of CA19-9 for the diagnosis of pancreatic cancer, the median sensitivity was 79% (70-90%) and the median specificity was 82% (68-91%) (14). It is a sialylated Lewis blood group antigen and its secretion is influenced by Lewis antigen phenotypes (13). The elevation of CA19-9 expression levels has also been observed in other conditions, including biliary obstruction and inflammation, digestive tract inflammation and other gastrointestinal malignancies, which limits its clinical application in pancreatic cancer (13,14).

CA19-9 is not generally considered to be a diagnostic or prognostic biomarker in pNETs as the majority of pNETs

present with normal range of CA19-9 (15,16). Conversely, in view of its abnormal increased expression level in common pancreatic cancer; CA19-9 has been used as a diagnostic marker to differentiate pancreatic cancer from pNETs (15,16). However, few previous studies have demonstrated that CA19-9 may be used as a prognostic biomarker in neuroendocrine tumors (17,18). For example, Elisei *et al* (17) reported a case of multiple endocrine neoplasia type 2B with significant elevation of CA19-9 expression levels. The patient experienced rapid disease progression and survived for only a short period, indicating that CA19-9 may be a biomarker of aggressiveness (17). A further study conducted by Elisei *et al* (18) revealed that 16/100 advanced structural recurrent/persistent medullary thyroid cancer tissues exhibited high expression levels of CA19-9, and the CA19-9 positive group demonstrated a higher mortality rate compared with the normal CA19-9 expression group.

The aim of current study was to evaluate the role of serum CA19-9 expression levels as a prognostic factor in a relatively large cohort of patients with pNETs at various clinical stages. Potential factors associated with abnormally increased expression levels of CA19-9 in pNETs were also investigated.

## Materials and methods

*Study design and treatment*. Patients (156 cases) were retrospectively retrieved from a single institution (Shanghai Cancer Center, Fudan University, Shanghai, China) between June 2006 and February 2015. The male-female ratio was ~1.1:1, with a mean age of 53 (range, 15-77). Specimens were collected prior to initiating major treatment by the Tissue Bank, Shanghai Cancer Center (Shanghai, China). The enrollment criteria included subjects who had baseline CA19-9 information. In addition, patients were included if they had complete demographics information. Patients were excluded if the diagnosis of pNET was not pathologically confirmed. All the cases were staged according to the modified European Neuroendocrine Tumor Society Tumor-Node-Metastasis (TNM) staging system (19). Tumors were classified as G1, G2 or G3 according to the 2010 World Health Organization classification (based on the mitotic index and the Ki-67 index) (20). All clinical and pathological data were collected from patient medical records obtained from the Shanghai Cancer Center, Fudan University. Incidental pNETs were detected during health check-ups or evaluations for unassociated symptoms (15). Functional pNETs were also included in incidental pNETs in the present study. The primary end point was set as overall survival. Follow-up information was updated in December 2016, with a median follow-up time of 32 months. Survival time was determined from the date of final diagnosis to the date of the last follow-up or mortality. The present study was approved by the Ethical Committee of Shanghai Cancer Center, Fudan University. Informed written consent was obtained from all patients prior to enrollment in the current study.

*CA19-9 evaluation*. Serum CA19-9 expression levels were examined within 2 weeks prior to major treatment initiation using an electrochemiluminescence immunoassay on the Roche Cobas e601 (Roche MODU D+P model, D2400-P800) immunoassay analyzer (Roche Diagnostics GmbH, Mannheim, Germany) according to the manufacturer's protocol. The recommended upper limit for the serum CA19-9 expression level was <37 U/ml. CA19-9 has been reported to be affected by biliary obstruction, inflammation and other conditions (14); thus, all patients with serum bilirubin >2 mg/ml, biliary obstruction and inflammation, digestive tract inflammation or other gastrointestinal malignancies at the time of CA19-9 evaluation were excluded (165 cases were included at the start and 156 cases were included subsequent to the exclusions).

Table I. Demographics and clinical characteristics.

| Demographic/clinical characteristics | Patients, n (%) |
|---|---|
| Age | |
| ≤50 years | 69 (44.2) |
| >50 years | 87 (55.8) |
| Gender | |
| Male | 73 (46.8) |
| Female | 83 (53.2) |
| Location | |
| Head | 65 (41.7) |
| Other | 91 (58.3) |
| Size | |
| ≤3 cm | 53 (34.0) |
| >3 cm | 103 (66.0) |
| TNM stage | |
| I, II | 102 (65.4) |
| III, IV | 54 (34.6) |
| Grade | |
| G1, G2 | 114 (73.1) |
| G3 | 16 (10.3) |
| Unknown | 26 (16.7) |
| Functional | |
| Positive | 15 (9.6) |
| Negative | 141 (90.4) |
| Symptomatic | |
| Positive | 92 (59.0) |
| Negative | 64 (41.0) |

TNM, tumor-node-metastasis.

*Statistical analysis*. The receiver operating characteristic (ROC) curve and area under the ROC curve were used to select the optimal cut-off values for baseline CA19-9 expression levels. Time-to-event variables were determined using the Kaplan-Meier method. Arms stratified by potential prognostic factors (age, gender, size, location, TNM stage, CA19-9 levels, grade and symptom) were analyzed by the log-rank tests. The Cox's proportional hazard ratio (HR) with a 95% confidence interval (CI) was used to estimate the difference between the stratified arms using the Stata® version 12.0 statistical software package (StataCorp LP, College Station, TX, USA). Categorical data were analyzed

Table II. Univariate and multivariate analysis for overall survival of all patients using the Cox proportional hazards model.

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| Characteristic | HR | 95% CI | P-value | HR | 95% CI | P-value |
| Age | | | | | | |
| ≤50 | 1 | / | / | | | |
| >50 | 0.82 | 0.40-1.67 | 0.581 | | | |
| Gender | | | | | | |
| Male | 1 | / | / | | | |
| Female | 0.52 | 0.25-1.08 | 0.075 | | | |
| Size (cm) | | | | | | |
| ≤3 | 1 | / | / | | | |
| >3 | 1.88 | 0. 81-4.38 | 0.135 | | | |
| Location | | | | | | |
| Head | 1 | / | / | | | |
| Other | 1.16 | 0.56-2.41 | 0.682 | | | |
| TNM stage | | | | | | |
| I, II | 1 | / | / | 1 | / | / |
| III, IV | 5.08 | 2.42-10.67 | <0.001 | 2.88 | 1.20-6.93 | 0.018[a] |
| CA19-9 (U/ml) | | | | | | |
| ≤16 | 1 | / | / | 1 | / | / |
| >16 | 2.60 | 1.28-5.28 | 0.006 | 1.52 | 0.70-3.29 | 0.286 |
| Grade | | | | | | |
| G1, G2 | 1 | / | / | 1 | / | / |
| G3 | 13.43 | 5.65-31.93 | <0.001 | 8.79 | 3.47-22.28 | <0.001[a] |
| Unknown | 3.10 | 1.25-7.69 | 0.015 | 1.77 | 0.65-4.80 | 0.262 |
| Incidental | | | | | | |
| Negative | 1 | / | / | | | |
| Positive | 0.67 | 0.30-1.45 | 0.295 | | | |

[a]P<0.05; TNM, tumor-node-metastasis; HR, hazard ratio; CI, confidence interval.

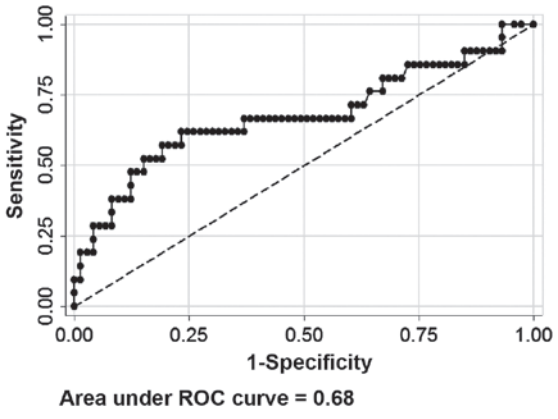


Figure 1. The ROC curve and area under the ROC curve for baseline carbohydrate antigen 19-9 expression levels as a prognostic factor. ROC, receiver-operating characteristic.

using Pearson's $\chi^2$ test or Fisher's exact test as appropriate. A two-sided P<0.05 was considered to indicate a statistically significant difference.

## Results

*Data and survival analysis of patients*. A total of 156 patients with pathologically confirmed pNETs were included in the final analysis (Table I). The male-female ratio was ~1.1:1, with 55.8% of patients being >50-years old (range, 15-77). A total of 65 (41.7%) patients had tumors located at the head of the pancreas and 53 (34.0%) patients had tumors <3 cm in diameter. In the current series, 65.4% of patients had stage I or II tumors. A majority (73.1%) of patients had G1 or G2 diseases, and 15 (9.6%) patients had functional diseases. For all the patients, ~59.0% of the patients had pNETs with symptoms and the other 41% were asymptomatic.

The selected cut-off value for CA19-9 as a prognostic predictor of pNETs was 16 U/ml by the ROC curve (area under ROC curve, 0.68; sensitivity 61.9%; specificity 76.7%; Fig. 1), with 32.7% of cases having CA19-9 expression levels higher than the cut-off value. A total of 8 (5.1%) cases had a CA19-9 expression level >100 U/ml and 22 (14.1%) cases were >37 U/ml. Univariate analysis was performed in order to evaluate factors associated with overall survival using the

Table III. Serum CA19-9 expression levels, patient demographics and clinical characteristics.

| Demographic or clinical characteristic | CA19-9 ≤16 U/ml | CA19-9 >16 U/ml | P-value |
|---|---|---|---|
| Age | | | 0.379 |
| ≤50 years | 49 | 20 | |
| >50 years | 56 | 31 | |
| Gender | | | 0.465 |
| Male | 47 | 26 | |
| Female | 58 | 25 | |
| Location | | | 0.931 |
| Head | 44 | 21 | |
| Others | 61 | 30 | |
| Size | | | 0.119 |
| ≤3 cm | 40 | 13 | |
| >3 cm | 65 | 38 | |
| TNM stage | | | 0.001[a] |
| I, II | 78 | 24 | |
| III, IV | 27 | 27 | |
| Grade | | | 0.075 |
| G1, G2 | 82 | 32 | |
| G3 | 8 | 8 | |
| Lymph status[b] | | | 0.057 |
| Positive | 12 | 10 | |
| Negative | 45 | 14 | |
| Vessel invasion[b] | | | 0.093 |
| Positive | 10 | 8 | |
| Negative | 41 | 15 | |
| Nerve invasion[b] | | | 0.429 |
| Positive | 7 | 5 | |
| Negative | 42 | 18 | |
| Functional | | | 0.085 |
| Positive | 13 | 2 | |
| Negative | 92 | 49 | |
| Symptomatic | | | 0.310 |
| Positive | 59 | 33 | |
| Negative | 46 | 18 | |

[a]P<0.05; [b]Cases that underwent curative resection only. TNM, tumor-node-metastasis; CA19-9, carbohydrate antigen 19-9.

Cox's proportional hazards model. The results demonstrated that TNM stage III or IV (HR=5.08; P<0.001), CA19-9 >16 U/ml (HR=2.60; P=0.006) and G3 diseases (HR=13.43; P<0.001) are adverse prognostic factors for patients' overall survival, whereas age, gender, tumor size and tumor location were not significantly associated with overall survival (Table II; Fig. 2). In multivariate analysis, TNM stage III or IV (HR=2.88; P=0.018) and G3 diseases (HR=8.79; P<0.001) were determined to be adverse prognostic factors for patients' overall survival (Table II).

*Parameters associated with baseline NLR levels*. A $\chi^2$ test was performed in order to compare clinicopathological characteristics between the CA19-9 ≤16 U/ml group and the CA19-9 >16 U/ml group (Table III). The CA19-9 >16 U/ml group had a significantly higher proportion of patients with TNM stage III/IV (P=0.001), but not age (P=0.379), gender (P=0.465), location (P=0.931), nerve invasion (P=0.429), functional (P=0.085) and symptomatic status (P=0.310). Although not statistically significant, the CA19-9 >16 U/ml group also demonstrated a trend to have a greater proportion of G3 tumors (P=0.075), positive lymph status (P=0.057), tumor size (P=0.119) and vessel invasion (P=0.093).

## Discussion

The present study determined the cut-off value for CA19-9 as a prognostic predictor of pNETs to be 16 U/ml, by ROC curve.

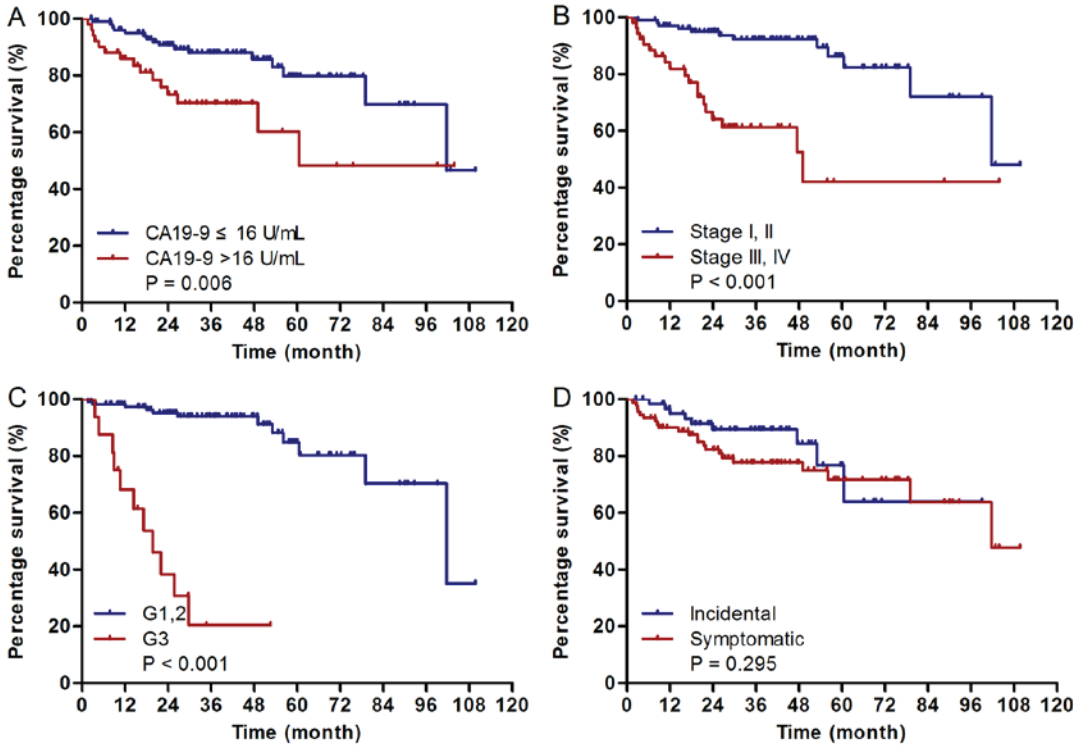


Figure 2. Kaplan-Meier survival curves for patients with pancreatic neuroendocrine tumors according to (A) CA19-9 expression levels (≤16 U/ml vs. >16 U/ml), (B) TNM stage (I, II vs. III, IV), (C) grade (G1, G2 vs. G3) and (D) symptoms (incidental vs. symptomatic). CA19-9 >16 U/ml (P=0.006), TNM stage III or IV (P<0.001) and G3 diseases (P<0.001) are adverse prognostic factors for patients' overall survival, whereas symptomatic disease was not significantly associated with overall survival (P=0.295). CA19-9, carbohydrate antigen 19-9.

Univariate analysis demonstrated that CA19-9 >16 U/ml was an adverse prognostic factor for patients' overall survival. It was also revealed that the CA19-9 >16 U/ml group had a statistically higher proportion of TNM stage III/IV, as compared with the CA19-9 ≤16 U/ml group. These findings indicate that CA19-9 may be a prognostic biomarker of pNETs, which may be able to reflect the aggressiveness and severity of the disease.

Chromogranin A (CgA) is currently the most widely used and most characterized biomarker of pNETs, and is detected in the circulation (16,21-23). In contrast to CgA, which is known to be elevated in well- and moderately-differentiated NETs (23), the present study demonstrated that increased CA19-9 expression levels indicated s poor prognosis, G3 disease, advanced stage and aggressive features. Therefore, for cases with abnormal elevation of the CA19-9 expression level, active treatment, including surgical resection and adjuvant treatments, and close follow-up must be strongly recommended and observation alone should not be used. In addition, CA19-9 may supplement CgA as a prognostic biomarker for pNETs. Furthermore, CgA should be combined with CA19-9 to reflect the tumor volume and severity of pNETs.

Compared with symptomatic non-functional pNETs, incidental pNETs are more frequently <2 cm in diameter, stage T1, node negative, grade I and associated with improved prognosis (15). Cheema *et al* (15) evaluated 143 patients with stage I-III pNETs, and the 5-year progression-free survival rate of incidentally diagnosed tumors was significantly higher compared with symptomatic tumors (86.0 vs. 59.0%; P=0.007). The present study revealed that 41.0% of pNETs were incidental pNETs, and these demonstrated no significantly improved survival compared with symptomatic tumors (HR=0.67; P=0.295), contrary to the results of a previous study (15).

In the present study cohort, only 8 (5.1%) cases had a CA19-9 expression level >100 U/ml and 22 (14.1%) cases were >37 U/ml, which is a lower frequency compared with that in pancreatic cancer (14). However, the use of CA19-9 as a differentiating diagnostic marker for pancreatic cancer must be utilized with caution, as >14% of pNETs were found to have aberrant CA19-9 secretion (>37 U/ml). The molecular mechanisms underlying the abnormal elevation of CA19-9 expression levels in pNETs are largely undefined. Previous studies have demonstrated that CA19-9 abnormal secretion may be explained by tumor hypoxia and glycosylation (24,25). The observation that CA19-9 was correlated with TNM stage and vessel invasion in pNETs in the present study also indicates that tumor hypoxia and glycosylation may be potential associated mechanisms. Further studies are required in order to confirm this hypothesis.

In the present study, pNETs with a CA19-9 >16 U/ml demonstrated a trend towards having a higher proportion of G3 tumors, as compared with pNETs with a CA19-9 ≤16 U/ml (P=0.075). G3 pNETs are well known for their aggressiveness and poor response to major treatment strategies, including surgery (26). Considering the differing management strategy between G1, G2 and G3 pNETs in clinical practice, the aberrant elevation of CA19-9 may serve as an indication of G3 pNETs for clinicians (26). However, further studies with larger sample cohort are required.

The novelty of the present study is in that, to the best of our knowledge, it is the first to reveal that CA19-9 is a

prognostic biomarker of pNETs, which may be able to reflect poor prognosis, advanced stage and aggressive characteristics. This result is in contrast to the results of a previous study that indicated that CA19-9 has limited value in the management of pNETs (27). In addition, CA19-9 may supplement CgA as a biomarker to guide the management of pNETs. However, as the present study was retrospective, the results must be interpreted with caution. Further prospective studies with larges sample sizes are urgently required in order to confirm these findings.

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